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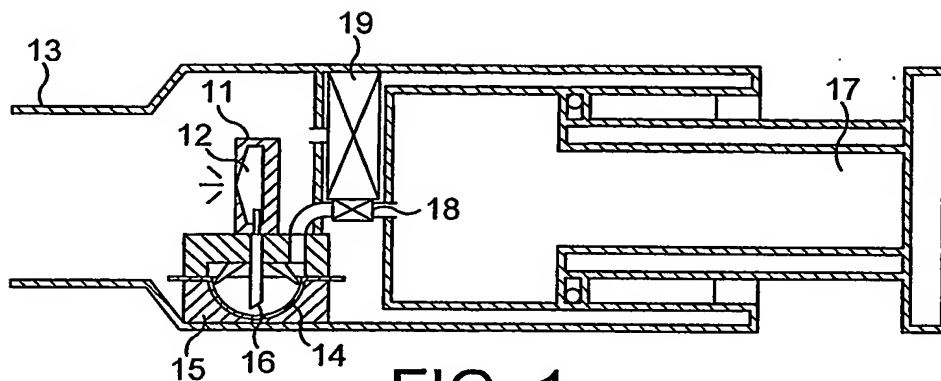


FIG. 1

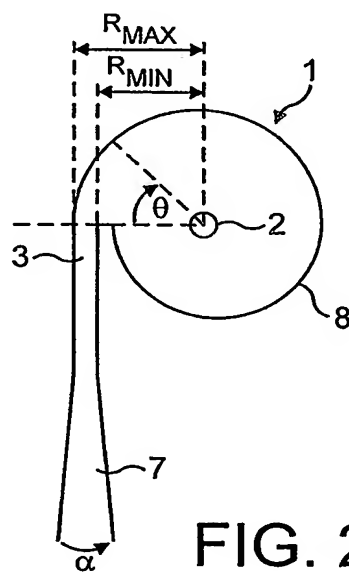


FIG. 2

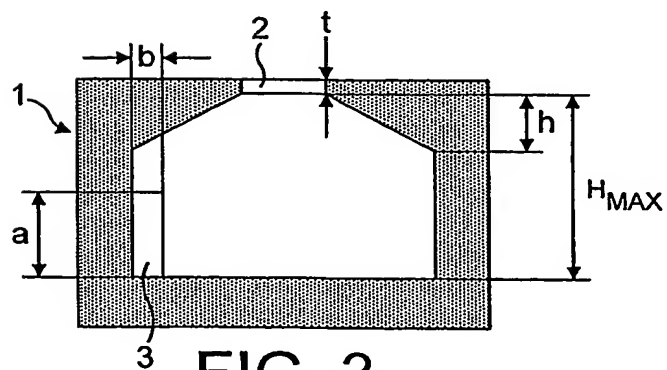


FIG. 3

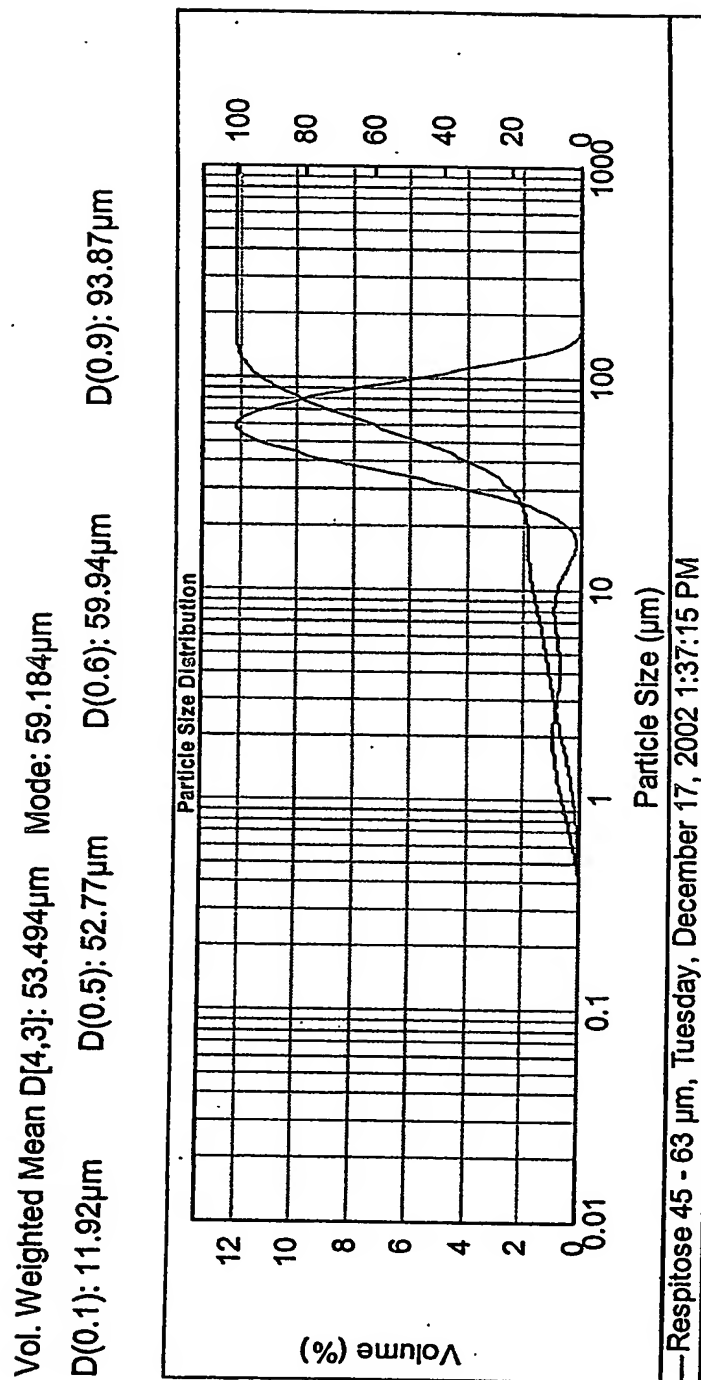


FIG. 4A

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Vol. Weighted Mean D[4,3]: 53.82 μ m Mode: 57.31 μ m
 D(0.1): 8.57 μ m D(0.5): 53.65 μ m D(0.6): 59.54 μ m D(0.9): 87.15 μ m

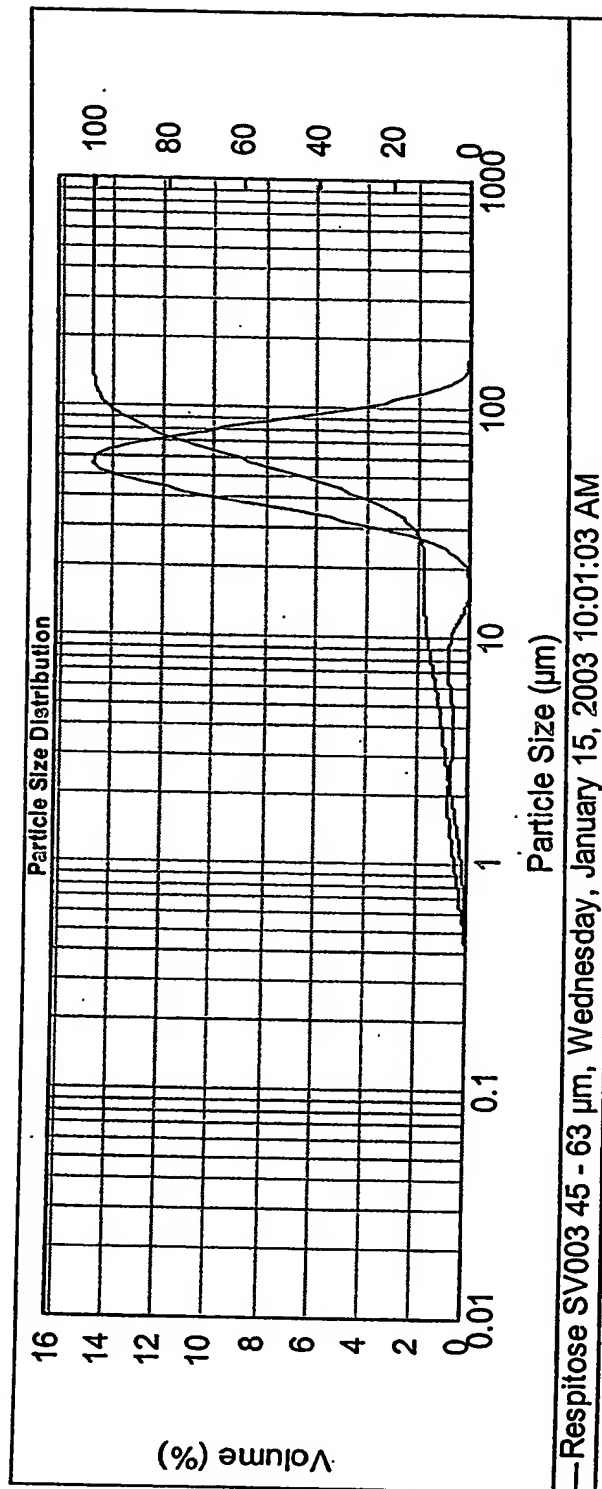


FIG. 4B

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Vol. Weighted Mean D[4,3]: 2.59 μ m Mode: 2.49 μ m
 D(0.1): 1.03 μ m D(0.5): 2.28 μ m D(0.6): 2.55 μ m D(0.9): 4.56 μ m

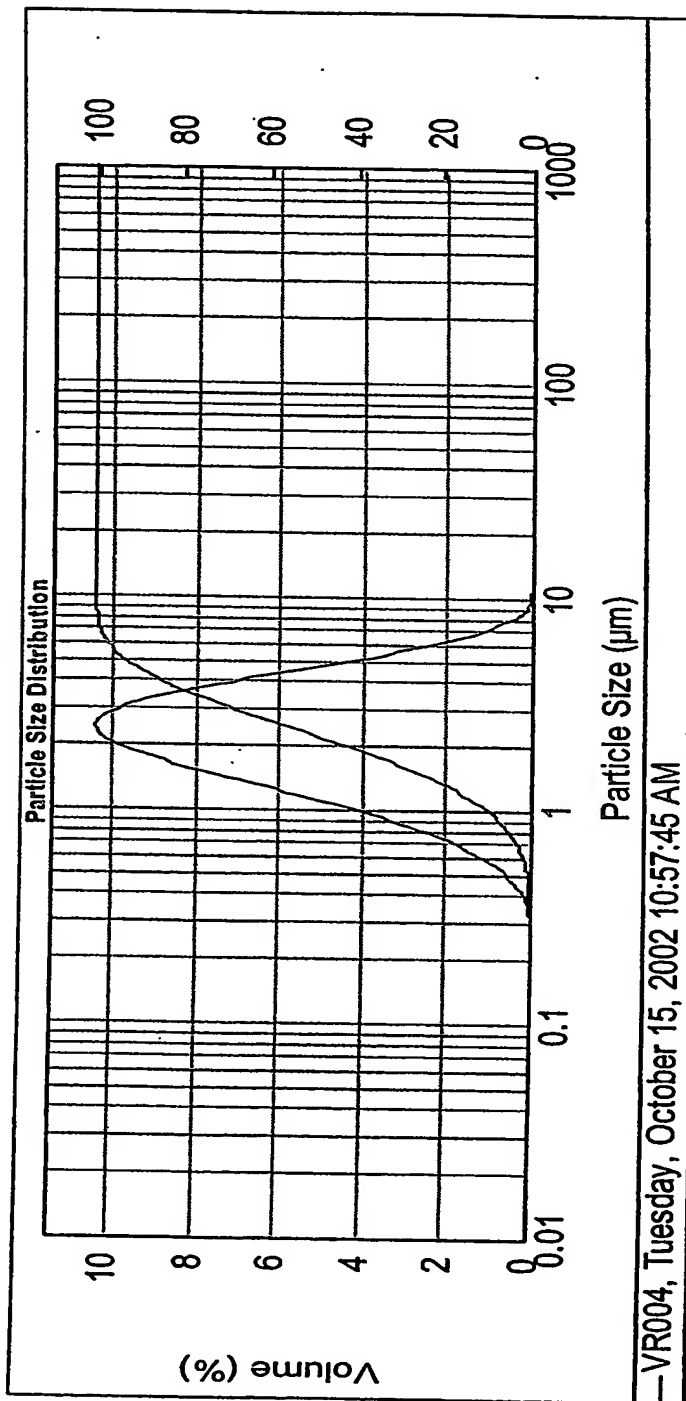
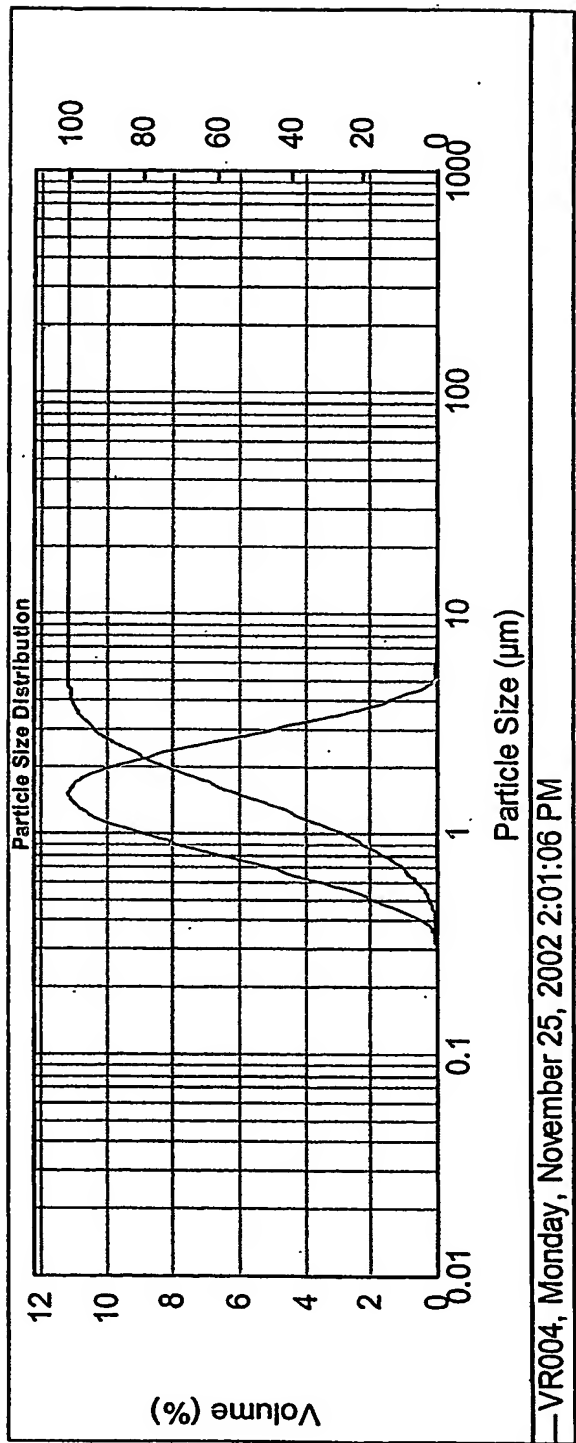


FIG. 5A

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Vol. Weighted Mean D[4,3]: 1.62 μ m Mode: 1.52 μ m
D(0.1): 0.73 μ m D(0.5): 1.45 μ m D(0.6): 1.67 μ m D(0.9): 2.770 μ m



—VR004, Monday, November 25, 2002 2:01:06 PM

FIG. 5B

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Stability Condition	Formulation	Assay	Related Substances (Highest Individual Peak %)	Related Substances (Sum of Related Peaks)
Initial		Initial	Initial	Initial
	Batch 1	ND	0.03	0.7
	Batch 2	ND	0.04	0.10
	Batch 3	101	0.03	0.07
	Batch 4	101	0.04	0.09
25°C / 60% RH		1 month	1 month	1 month
	Batch 1	99	0.04	0.10
	Batch 2	99	0.06	0.20
	Batch 3	99	0.05	0.20
	Batch 4	99	0.05	0.14
40°C / 75% RH		1 month	1 month	1 month
	Batch 1	98	0.04	0.14
	Batch 2	100	0.08	0.20
	Batch 3	99	0.04	0.14
	Batch 4	98	0.13	0.28

FIG. 6A

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Timepoint	Assay ¹	Related Substances	Uniformity of Delivered Dose ²			Aerodynamic Assessment ³		
	(%)	Total ⁴ (%)	Largest (%)	Mean (µg)	Range (µg)	Delivered (µg)	FPD ³ (µg)	FPF ³ (µg)
Initial	Batch 1	103 ¹	<0.1	172	157-186	175	118	67
	Batch 2	100 ¹	<0.1	170	159-181	170	105	62
	Batch 3	101 ¹	<0.1	172	160-180	172	117	68
	Batch 4	99 ¹	<0.1	173	149-190	161	109	68
	Batch 4	ND	ND	182	166-191	ND	ND	ND
1 month (25°C/60% RH)	Batch 1	99	<0.1	163	143-181	160	108	67
	Batch 2	99	<0.1	164	152-175	157	91	58
	Batch 3	98	<0.1	166	146-176	158	98	62
	Batch 4	102	<0.1	144 ⁶	135-153	140	88	63
1 month (40°C/75% RH)	Batch 1	98	<0.1	ND	ND	161	107	67
	Batch 2	99	<0.1	ND	ND	161	89	56
	Batch 3	98	0.1	ND	ND	162	100	62
	Batch 4	103	<0.1	ND	ND	145	83	57
2 month (25°C/60% RH)	Batch 4	ND	ND	157	139-176	139	84	60
3 month (25°C/60% RH)	Batch 1	97	<0.1	169	155-185	152	90	59
	Batch 2	99	<0.1	160	127-177	156	85	54
	Batch 3	98	<0.1	175	165-185	156	95	61
	Batch 4	101	<0.1	155	129-174	146	101	69

¹ Assay as % nominal w/w. Initial results are from blend content uniformity test. Subsequent results are assays of powder from 5 blisters

² Uniformity of delivered dose determined on 11 doses, mean reported for dose 2-11, range for all doses.

³ Aerodynamic assessment of fine particles by ACI at 60 L min⁻¹ ≤5µm. FPD=Fine Powder Dose, FPF=Fine Powder Fraction. (n=2).

⁴ Total related substance peaks ≥0.02% wrt drug substance.

⁵ L1=Ph Eur standard for uniformity of delivered dose, 1st level, 9/10 75-125%, 10/10 65-135%, of mean.

⁶ L2=Ph Eur standard for uniformity of delivered dose, 2nd level, 10/10 65-135%, of mean.

⁷ Uniformity of delivered dose determined on 10 doses, mean reported for dose 1-10, range for all doses.

ND=not determined

FIG. 6B

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Timepoint	Assay ¹	Related Substances		Uniformity of Delivered Dose ²			Aerodynamic Assessment ³		
		Total ⁴ (%)	Largest (%)	Mean (µg)	Range (µg)		Delivered (µg)	FPD ⁵ (µg)	FPF ⁶ (µg)
3 month (40°C/75% RH)	Batch 1	96	<0.1	ND	ND	ND	149	86	58
	Batch 2	98	<0.1	ND	ND	ND	155	85	55
	Batch 3	98	<0.1	ND	ND	ND	158	93	58
	Batch 4	102	<0.1	ND	ND	ND	151	96	63
6 month (25°C/60% RH)	Batch 1	97	<0.1	159	128-167	Pass L1	148	94	64
	Batch 2	98	<0.1	170	156-183	Pass L1	152	92	60
	Batch 3	98	<0.1	159	151-166	Pass L1	158	95	60
	Batch 4	101	<0.1	165	146-182	Pass L1	162	110	68
9 month (25°C/60% RH)	Batch 1	97	<0.1	168	161-179	Pass L1	155	111	71
	Batch 2	98	<0.1	170	152-177	Pass L1	168	98	59
	Batch 3	97	<0.1	167	152-173	Pass L1	164	107	65
	Batch 4	98	<0.1	159	120-172	Pass L1	150	87	58
12 month (25°C/60% RH)	Batch 1	97	<0.1	161	143-176	Pass L1	153	92	60
	Batch 2	98	<0.1	162	155-167	Pass L1	158	97	62
	Batch 3	98	<0.1	170	154-183	Pass L1	161	108	67

¹ Assay as % nominal w/w. Initial results are from blend content uniformity test. Subsequent results are assays of powder from 5 blisters

² Uniformity of delivered dose determined on 11 doses, mean reported for dose 2-11, range for all doses.

³ Aerodynamic assessment of fine particles by ACI at 60 L min⁻¹ ≤ 5µm. FPD=Fine Powder Dose, FPF=Fine Powder Fraction. (n=2).

⁴ Total related substance peaks ≥0.02% wrt drug substance.

⁵ L1=Ph Eur standard for uniformity of delivered dose, 1st level, 9/10 75-125%, 10/10 65-135%, of mean.

⁶ L2=Ph Eur standard for uniformity of delivered dose, 2nd level, 10/10 65-135%, of mean.

⁷ Uniformity of delivered dose determined on 10 doses, mean reported for dose 1-10, range for all doses.

ND=not determined

FIG. 6C

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Formulation Details 5000		Uniformity of Delivered Dose 6000 (DUSA, n=10)					Fine Particle Performance (<5µm cut-off) 7000 MSLI (ACI)								
		Drug Retention		DD (µg) 6015	Metered (µg) 6020	Mass balance (µg) 6025	n=	Drug Retention 7010		DD (µg) 7015	FPD (µg) 7020	FPF (%) 7025	Metered (µg) 7030	Mass balance (µg) 7035	Test Flow Rate (L min ⁻¹) 7036
		Blister (µg) 6012	Device (µg) 6013					Blister (µg) 7012	Device (µg) 7013						
		7.2	4.3	84	95	93	3 (1)	7.7 (7.5)	7.5 (7.2)	85 (76)	56 (52)	66 (68)	100 (91)	95 (88)	95 (95)
100µg 45-63µm Air Jet Inversina															
		7.3	3.6	85	95	92	3	4.4	5.7	82	55	66	92	89	95
100µg 45-63µm Air Jet Inversina															
				Not Done			3	6.9	8.6	78	39	50	93	94	95
100µg 45-63µm Grindomix															
				Not Done			3	5.4	6.3	86	40	47	97	96	95
100µg 45-63µm Grindomix															
				Not Done			3	4.2	9.4	83	52	62	97	92	95
100µg 20-30µm Grindomix															
		10.0	5.3	188	203	96	(2)	(7.8)	(14.5)	(175)	(122)	(70)	(197)	(94)	60
200µg 45-63µm Air Jet Inversina															

FIG. 7A

Formulation Details 5000		Uniformity of Delivered Dose 6000 (DUSA, n=10)					Fine Particle Performance (<5µm cut-off) 7000 MSLI (ACI)							
		Drug Retention 6010		Delivered Dose 6015		6020 Metered dose (µg)	Mass Balance 6025 (%)	Drug Retention 7010		DD (µg) 7015	Fine Particle		Metered (µg) 7030	Mass balance (µg) 7035
		Blister (µg) 6012	Device (µg) 6013	(µg) 6016	% nominal 6017			Blister (µg) 7012	Device (µg) 7013		FPD (µg) 7020	FPF (%) 7505		
100µg 45-63µm Inversina		6.6	7.8	81	81	95	95	8.8	5.6	82	52	64	96	96
200µg 45-63µm Inversina		12.1	11.5	170	85	194	93	9.8	13.3	175	118	67	198	96
200µg 45-63µm Inversina		9.2 14.5	12.7 8.6	162 169	81 85	184 192	93 96	6.5	15.2	170	105	62	192	96
200µg 45-63µm Inversina		11.0	11.2	171	85	193	95	10.7	14.1	172	117	68	196	96

Test Flow Rate = 60 L min⁻¹

FIG. 7

Vol. Weighted Mean D[4,3]: 3.41 μm Mode: 2.95 μm
D(0.1): 1.44 μm D(0.5): 2.91 μm D(0.6): 3.34 μm D(0.9): 5.77 μm

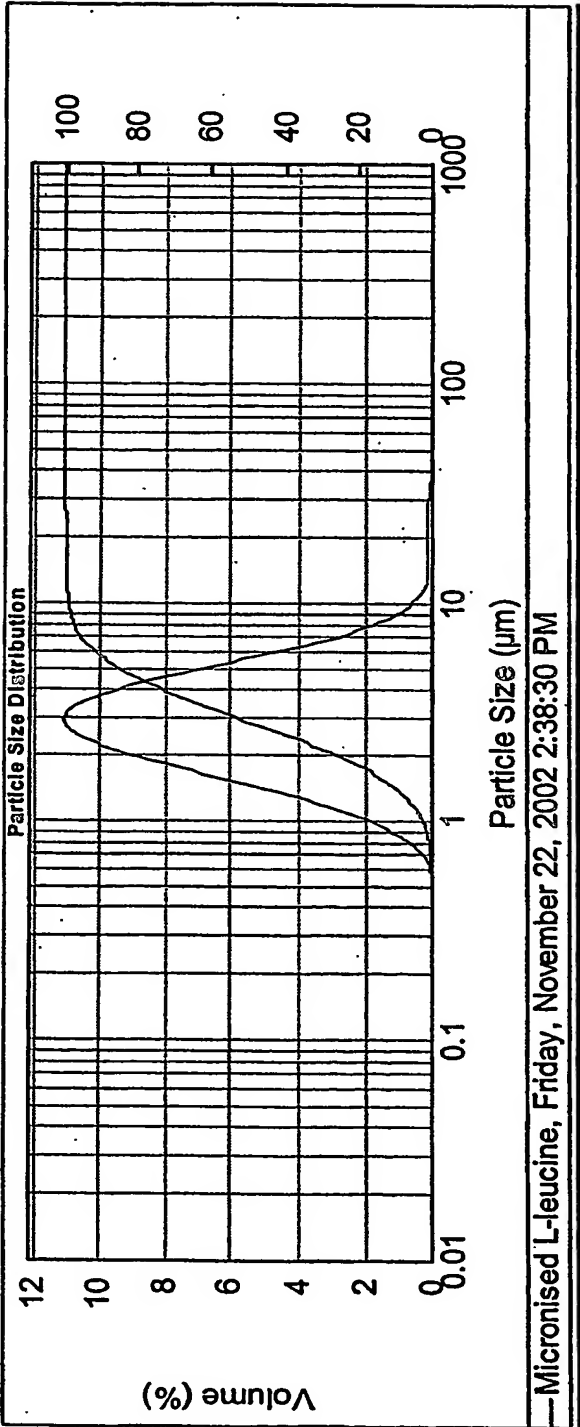


FIG. 8

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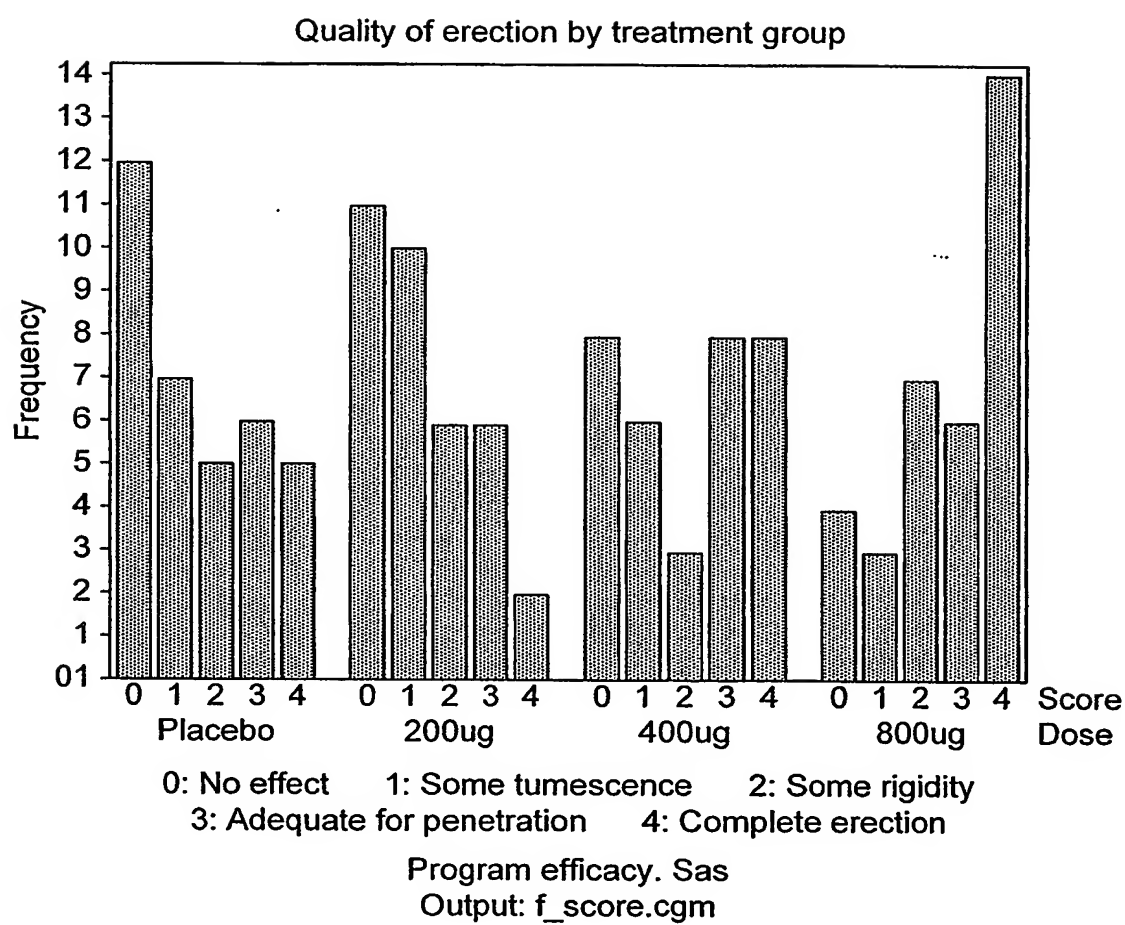


FIG. 9

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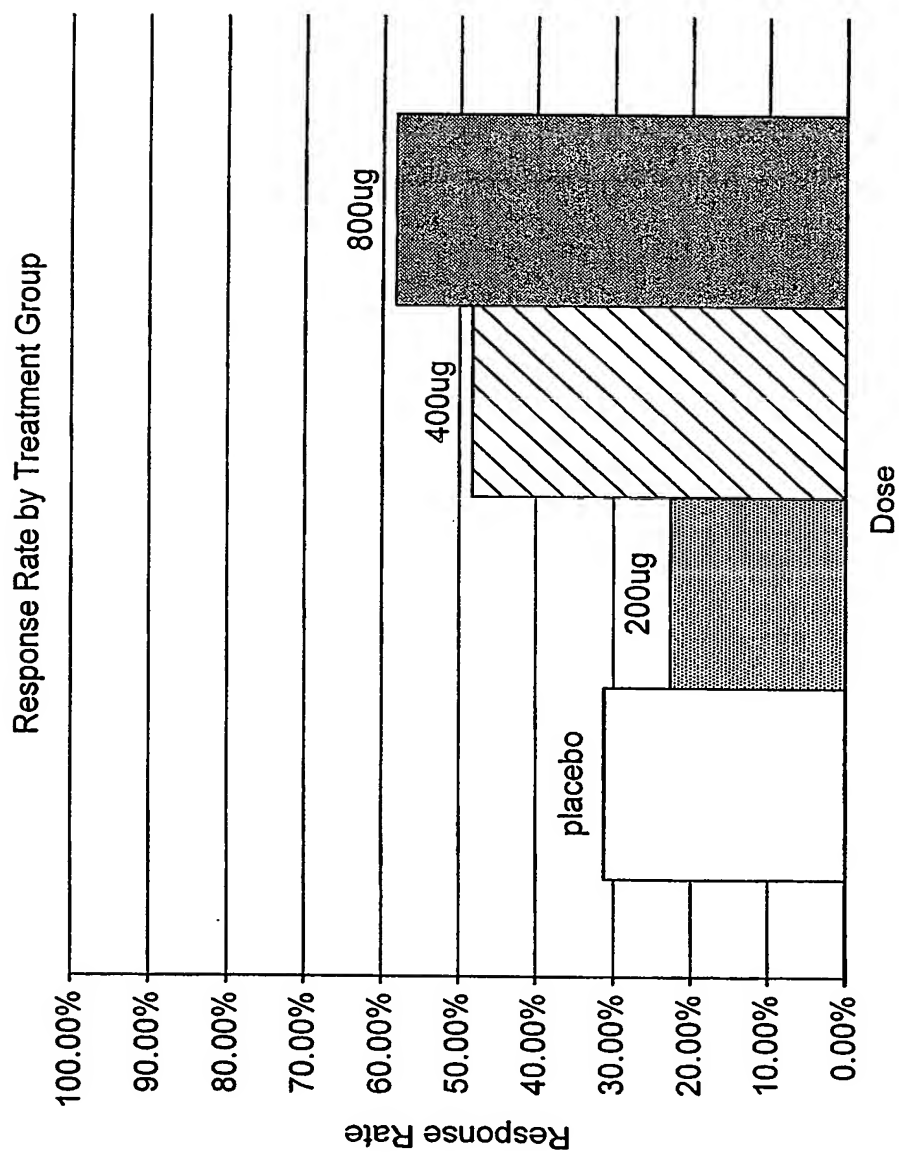


FIG. 10

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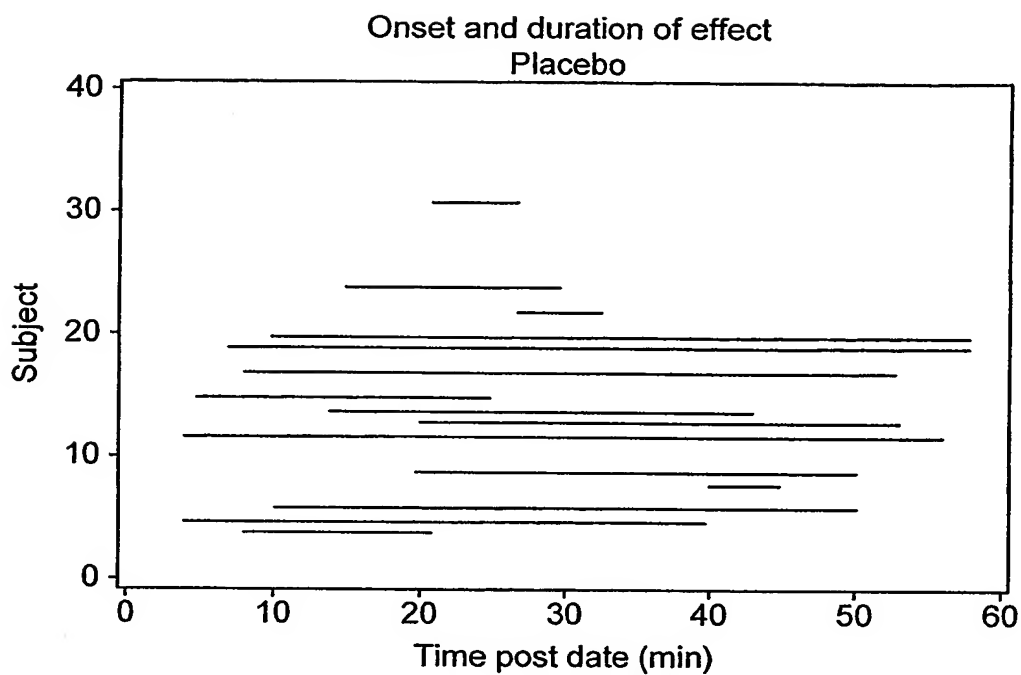


FIG. 11

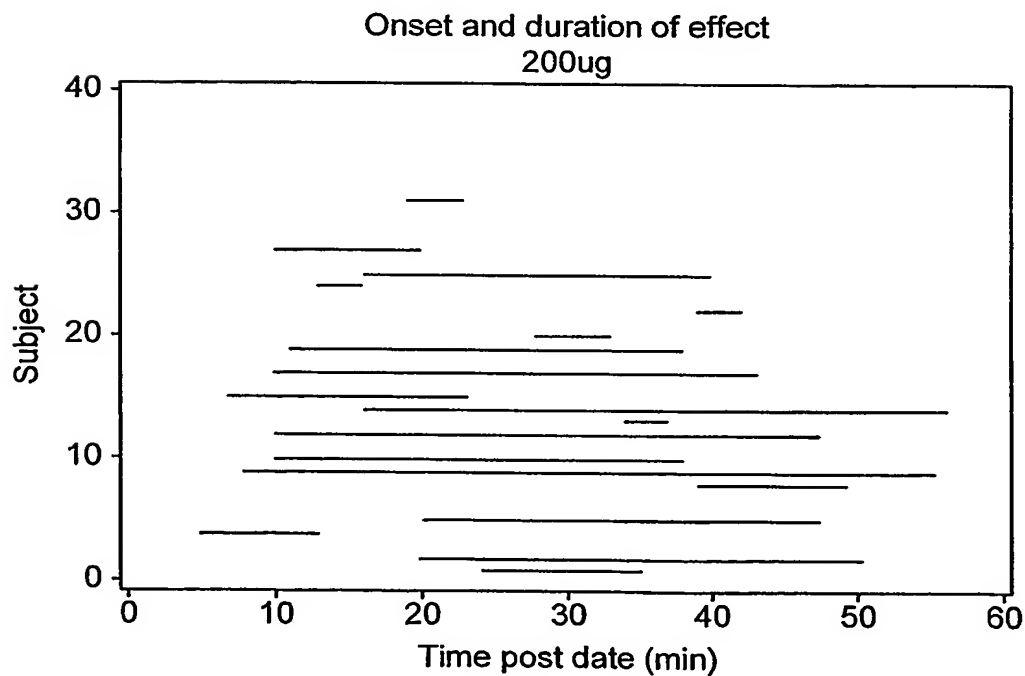


FIG. 12

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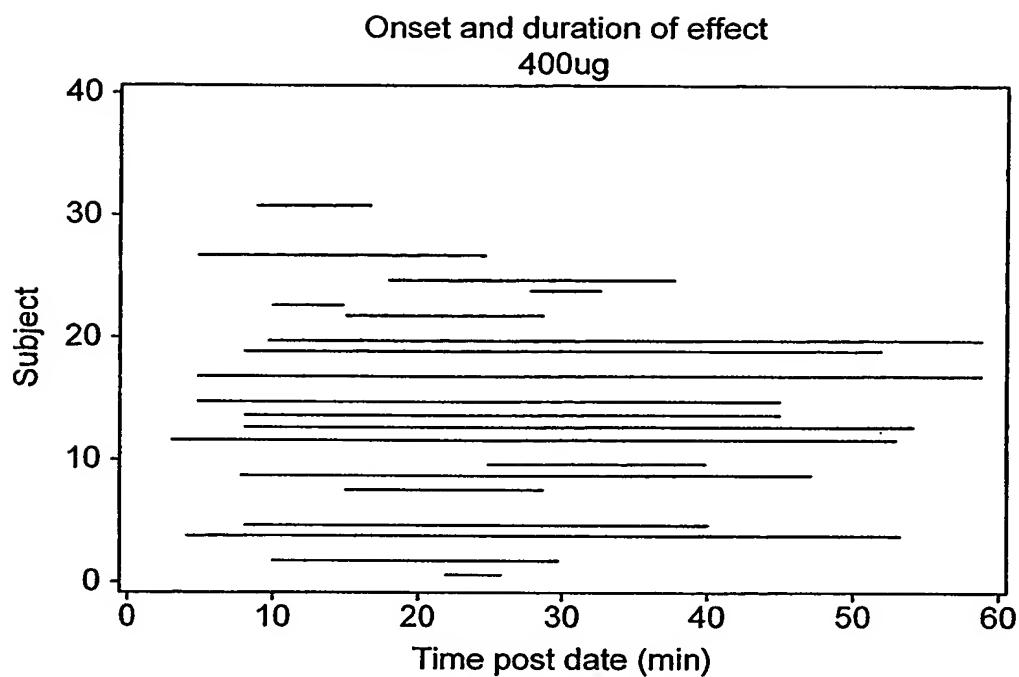


FIG. 13

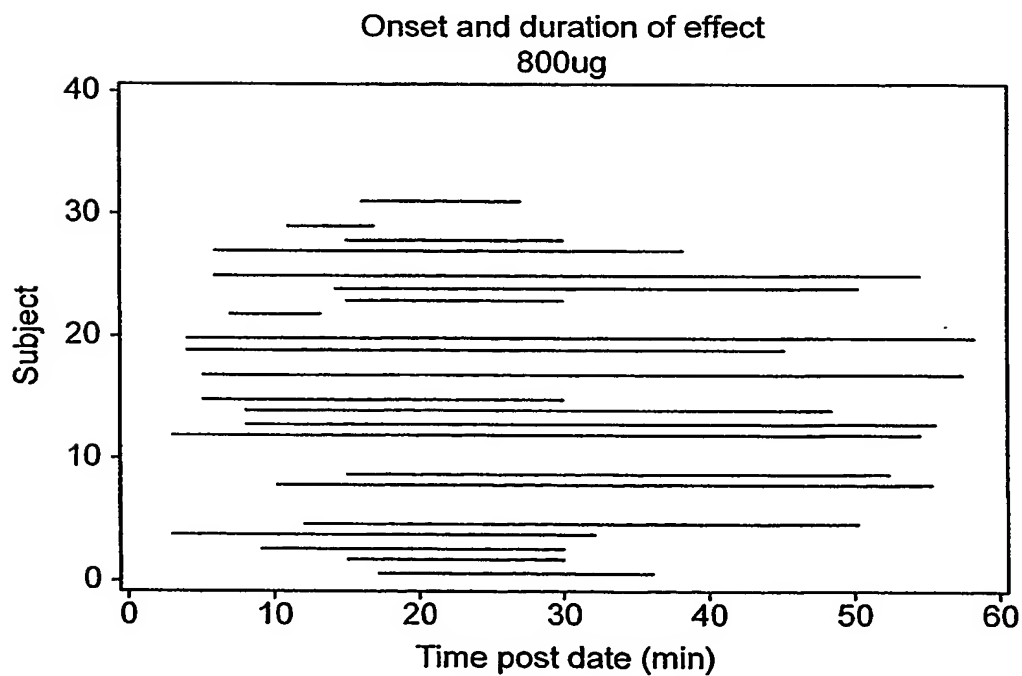


FIG. 14

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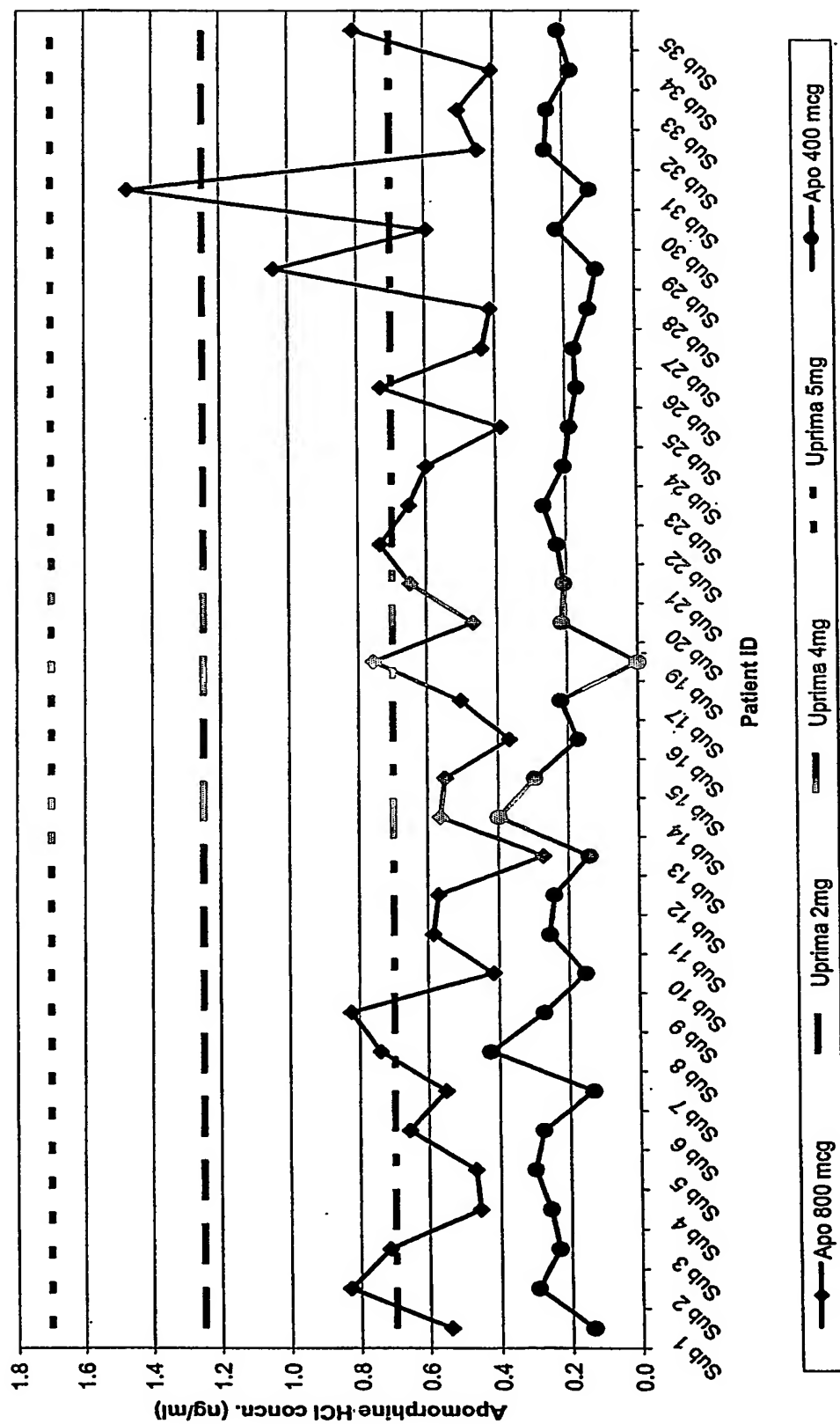


FIG. 15

Comparison of mean plasma concentration \pm standard error of mean
600 μg (n=13), 900 μg (n=16) and 1200 μg (n=5)

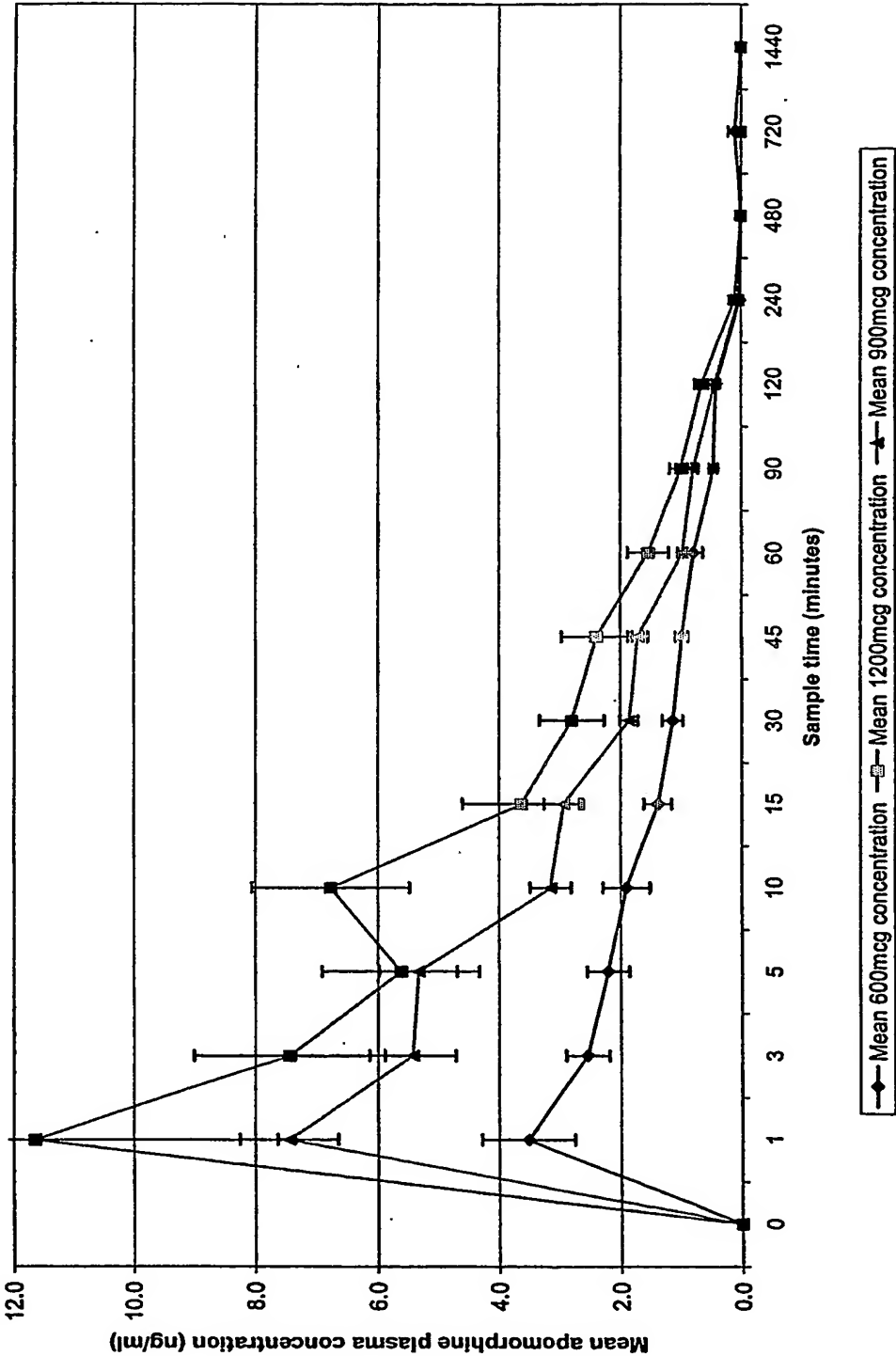


FIG. 16

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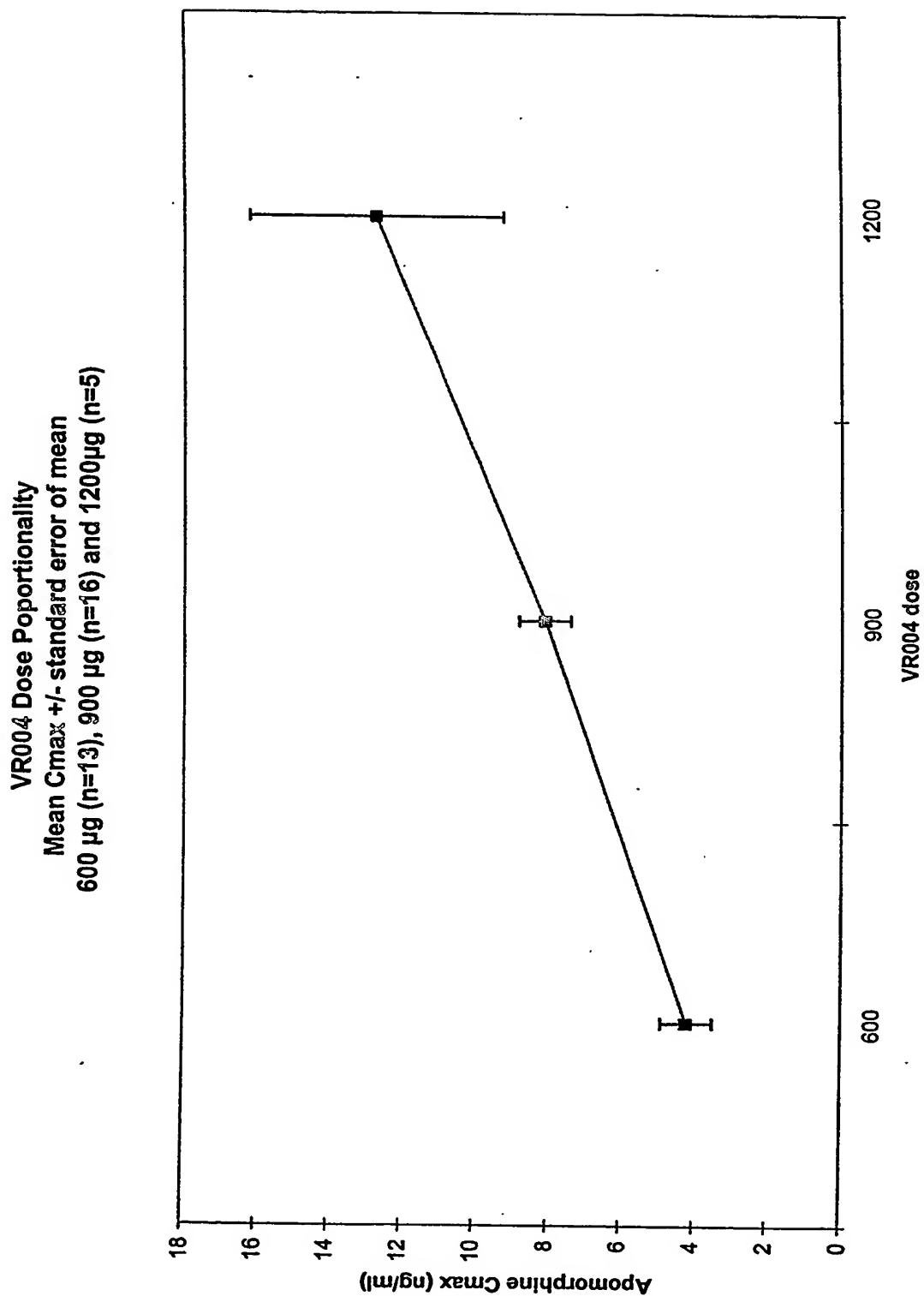


FIG. 17

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VR004 Dose Proportionality
Mean AUC_{0-4} +/- standard error of mean
600 μ g (n=13), 900 μ g (n=16) and 1200 μ g (n=5)

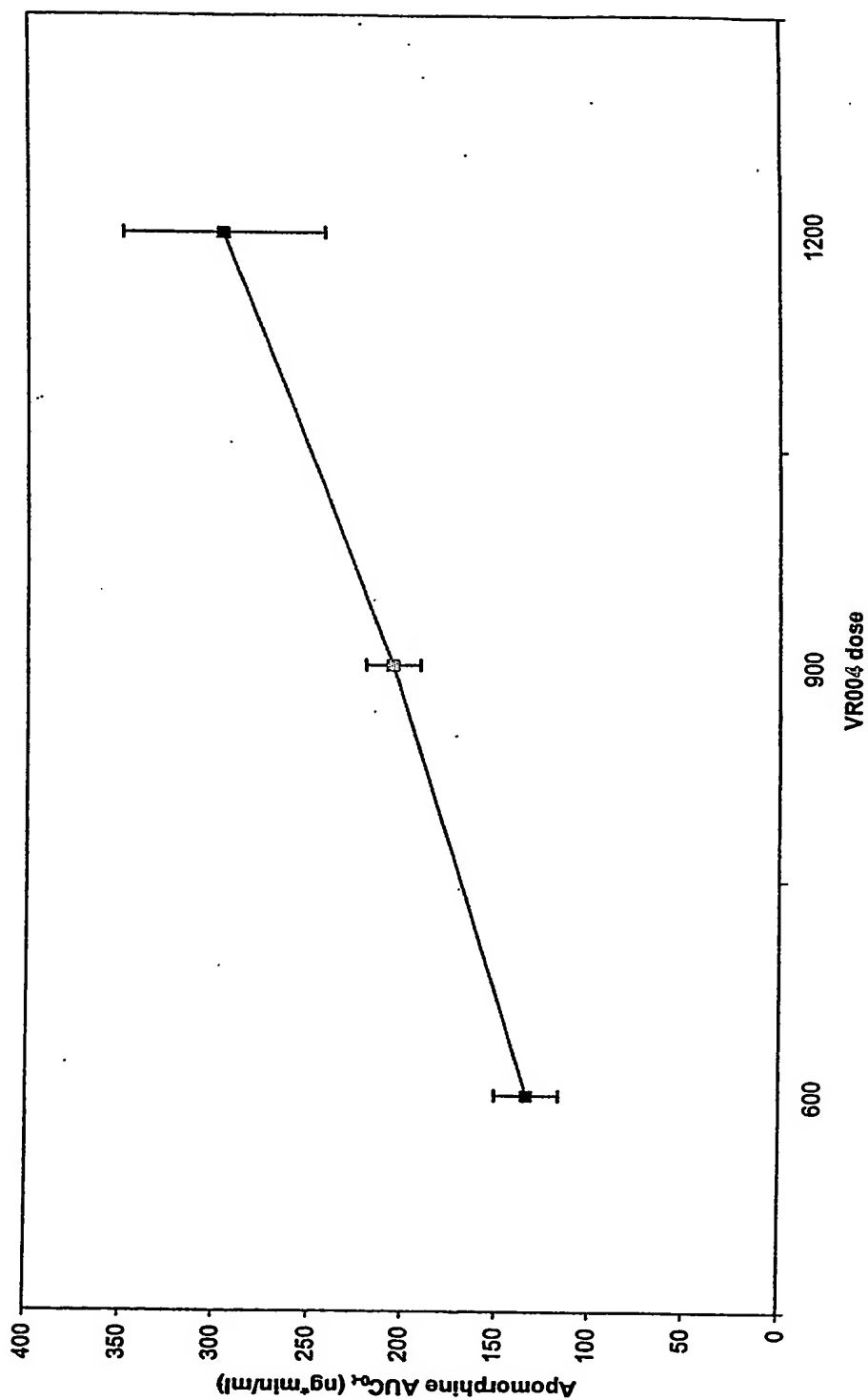


FIG. 18

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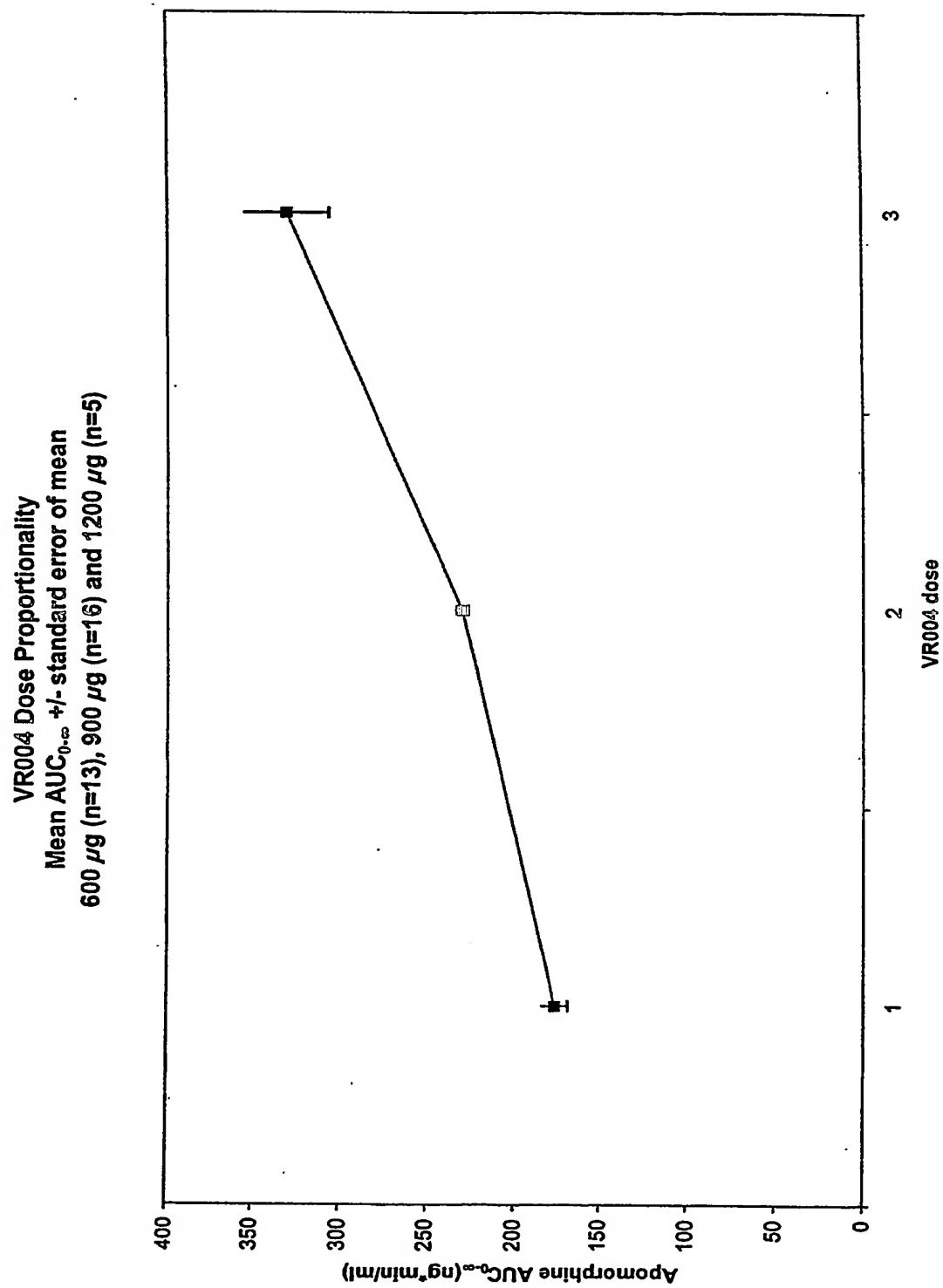


FIG. 19

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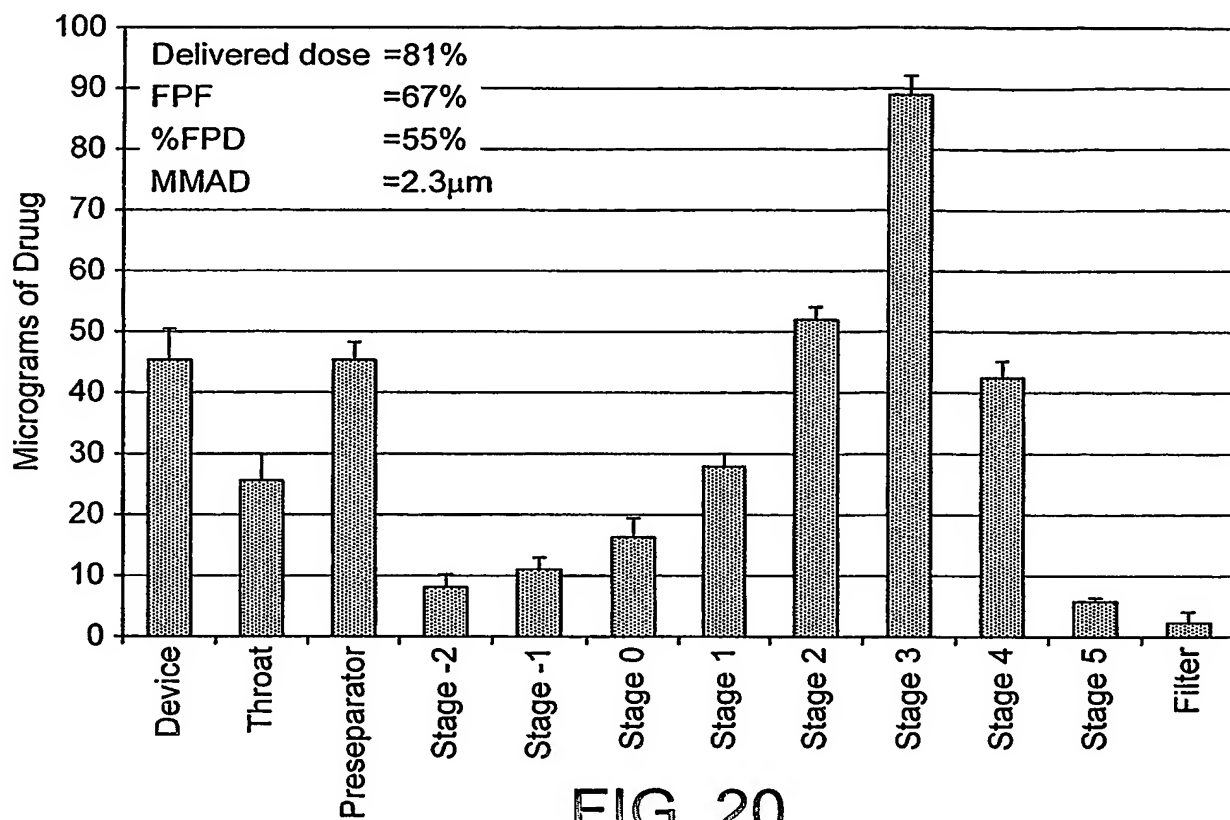


FIG. 20

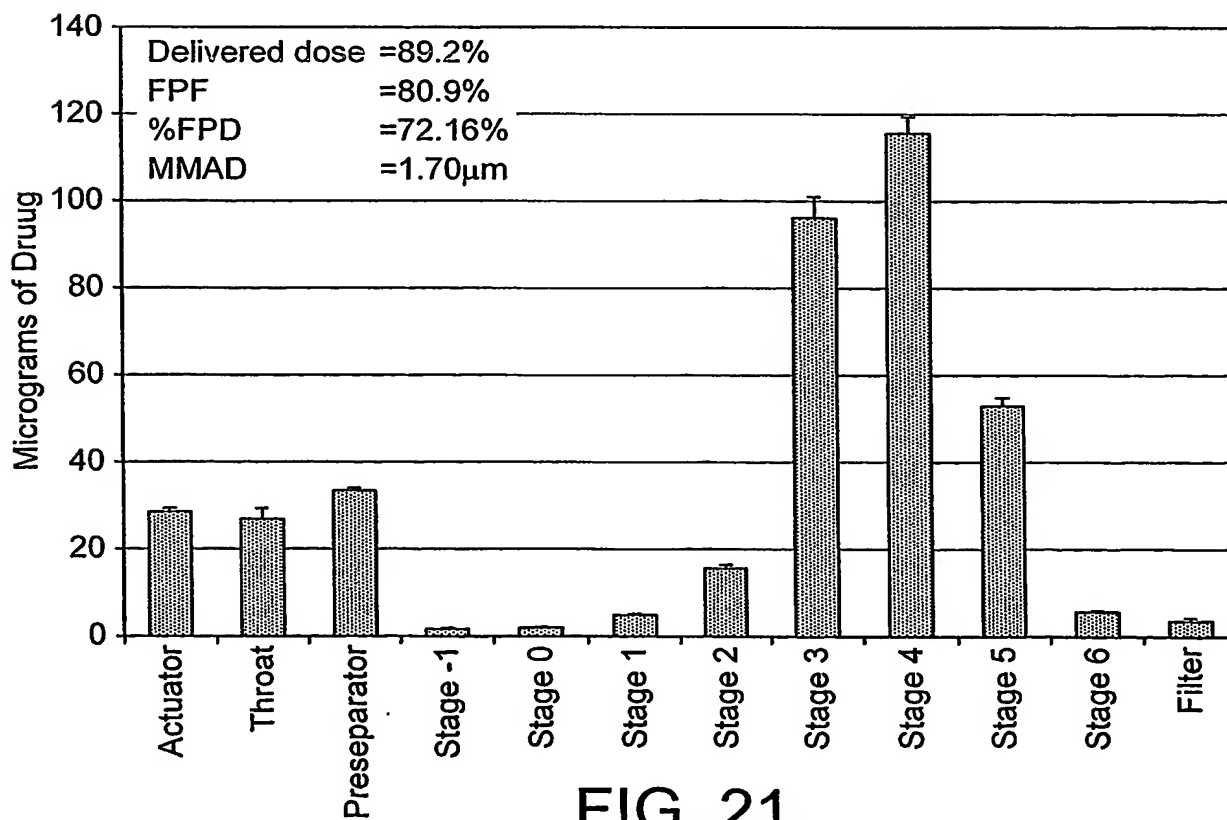
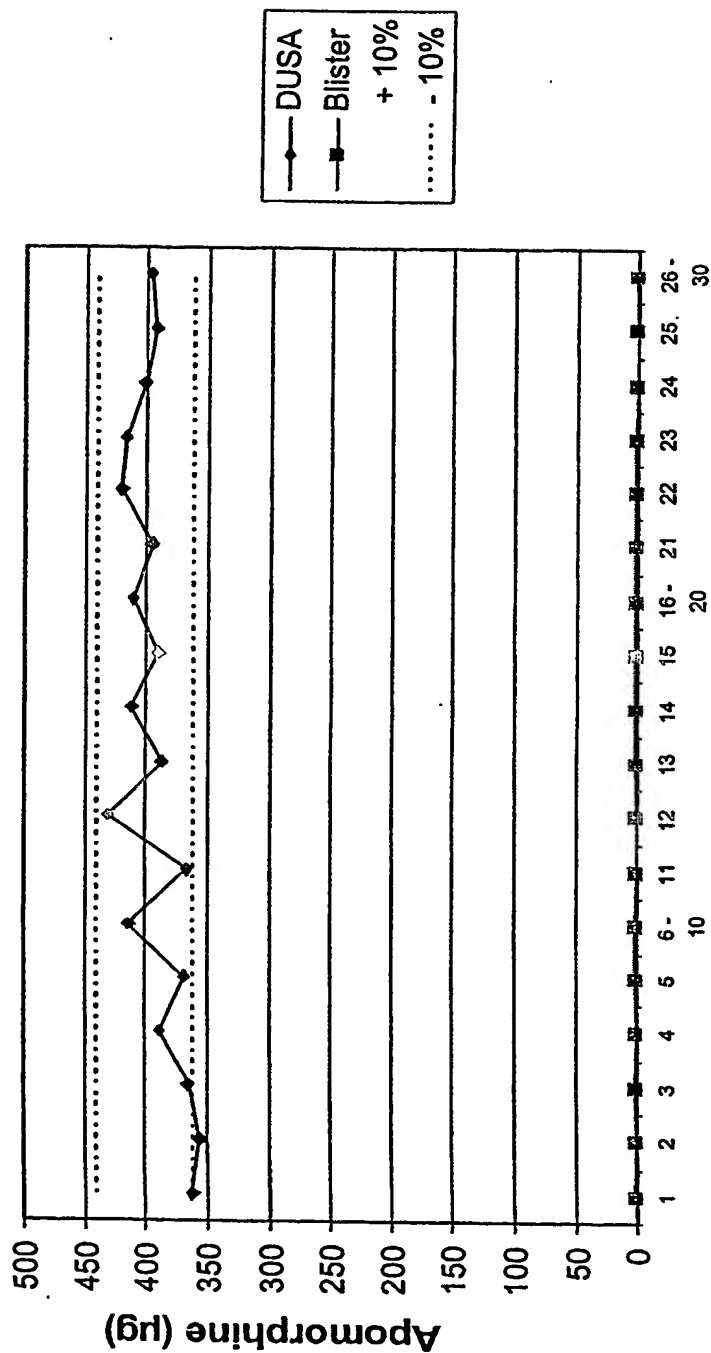


FIG. 21

30 Shot Through Life DUSA Study

Formulation 12A



Shot No.
(CL 1.60 l/min, 1.5 bar, 15ml reservoir, 2mg blister, 400ug Apomorphine)

FIG. 22

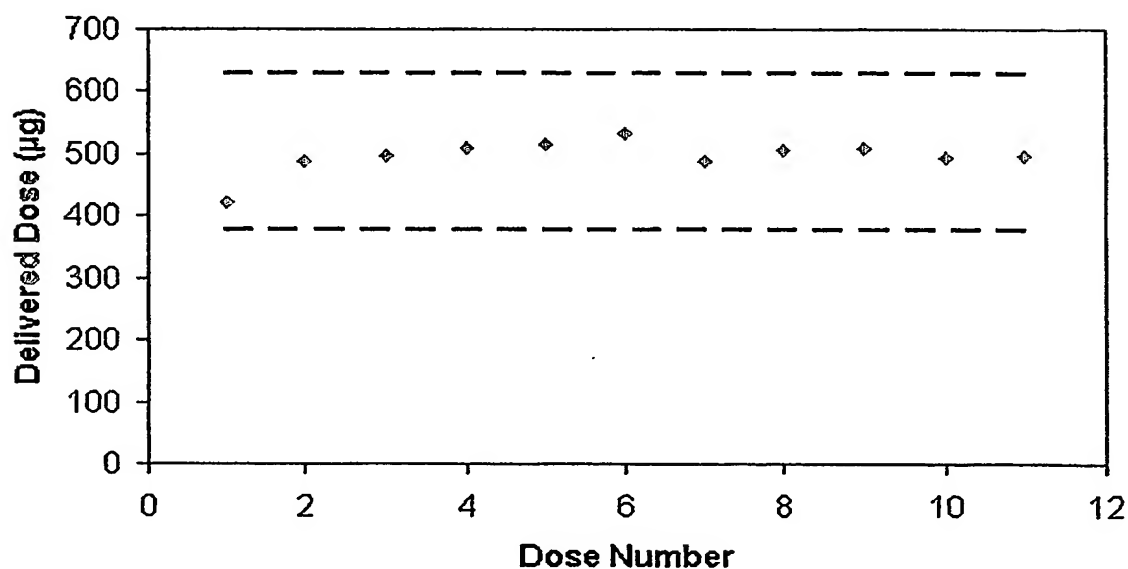
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Formulation Details

Drug: Apomorphine HCl
Dose (μg): 567.7352
Fill Weight (mg): 3

Device Details

Device: Aspirair
Pressure (bar): 1.5
Volume (ml): 15



Specification: 9/10 within $\pm 25\%$ of batch mean

Dotted lines are $\pm 25\%$ of mean (doses 2-11)

FIG. 23A

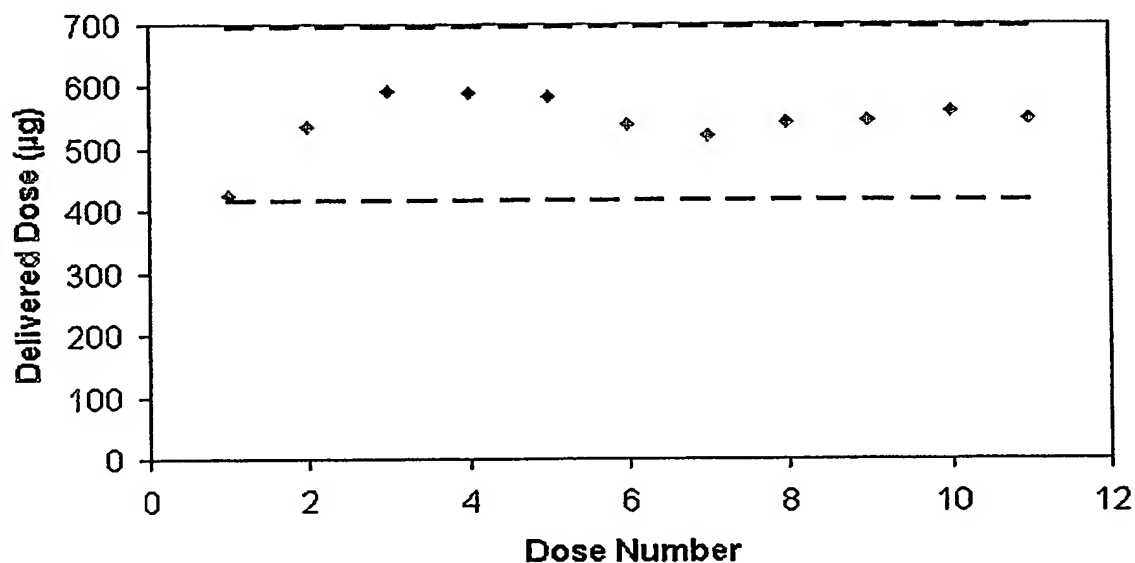
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Formulation Details

Drug: Apomorphine HCl
Dose (μg): 600
Fill Weight (mg): 3

Device Details

Device: Aspirair
Pressure (bar): 1.5
Volume (ml): 15



Specification: 9/10 within $\pm 25\%$ of batch mean

Dotted lines are $\pm 25\%$ of mean (doses 2-11)

FIG. 23B